are reagents that denature proteins. In this method, nucleic acids bind to a solid support made of an organic (i.e, carbon-based) polymer such as latex, polyurethane, or polystyrene, in the presence of a detergent and the absence of any chaotrope. A kit for practicing the method is also included within the scope of the invention.

Many conventional methods for binding nucleic acids to solid supports require the use of chaotropic agents. These agents are often hazardous and may interfere with many enzymatic reactions and other downstream biochemical manipulations. Thus, by eliminating the need for chaotropes, the invention provides tremendous advantages in nucleic acid isolation.

The Amendment

Pursuant to the Examiner's request, applicants have amended the specification to include a generic term with the Dynabeads® trademarked name. The generic term can be found at page 137 of the Technical Handbook published by the manufacturer in 1995. A copy of the page is attached hereto as Exhibit A. Other amendments were made to the specification to correct typographical errors.

Claim 1 is amended to specify that the solid support contains an organic polymer, and that the nucleic acid binds to the solid support in the presence of a detergent and absence of any chaotropic agent. These amendments are fully supported by applicants' disclosure. The specification teaches at page 9, lines 17 and 27, that the solid support can be made of a

polymeric material, e.g., latex; at page 11, line 1 (as amended), that the support can be made of polystyrene; and at page 11, line 11, that the solid support can contain polyurethane. Latex, polystyrene, and polyurethane are all organic polymers, i.e., carbon-based polymers. The specification also discloses, at page 5, top paragraph, that the invention eliminates the need for chaotropic agents in nucleic acid isolation. Indeed, chaotropic agents are not used in the working examples provided in the specification. Further, the specification teaches that the binding of nucleic acid to a solid support can be performed in the presence of a detergent. See the specification, e.g., at page 6, lines 22-25, and page 7, lines 5-8.

New claims 19-21 specify that the nucleic acid-binding solid support can be polyurethane, latex, or polystyrene. As discussed above, the specification teaches the use of these materials.

New claim 22 states that the solid support comprises superparamagnetic polystyrene beads. Support for this new claim appears in the specification at page 11, line 1 (as amended).

New claim 23 states that the solid support is porous. Support for this claim appears in the specification at page 9, line 24.

New claim 24 specifies that the nucleic acid bound to the solid support is used for further biochemical manipulation. Support for this new claim appears throughout the specification. See, e.g., Examples 1-13, which discuss such manipulations as

elution from the support, quantification, and polymerase chain reaction.

No new matter is introduced by the above amendment.

Pending Claims

Claims 1-24 are pending, new claims 19-24 having been added by the above amendment. Claims 1-18 were rejected on various grounds, discussed below.

Rejection 35 U.S.C. § 112, first paragraph

Claims 1-18 are rejected for alleged lack of enablement.

The examiner first asserts that the specification "mentions only one" solid support, i.e., Dynabeads® DNA DIRECT, that can be used in the claimed methods. See Office Action, page 2, first paragraph.

Contrary to this assertion, the specification discloses many different kinds of useful solid support. See the following quotation from page 9 of the specification:

> The solid support may be any of the well known supports or matrices which are currently widely used or proposed for immobilisation, separation etc. These may take the form of particles, sheets, gels, filters, membranes, fibres, capillaries, or microtitre strips, tubes, plates or wells etc.
>
> Conveniently the support may be made of glass, silica, latex or a polymerical material.

The specification further describes, at pages 10 and 11, that:

> Non-magnetic polymer beads suitable for use in the method of the invention are available from Dyno Particles AS (Lillestrøm, Norway) as well as from Qiagen, Pharmacia and Serotec . . . Especially preferred are superparamagnetic particles for example those described by Sintef in EP-A-106873 . . . The well-known magnetic particles sold by Dynal AS (Oslo, Norway) as Dynabeads® . . . are particularly suited to use in the present invention . . . Weakly and strongly positively charged surfaces, weakly negatively charged neutral surfaces and hydrophobic surfaces eg. polyurethane-coated have been shown to work well.

Clearly, the specification mentions many useful types of solid support which include such organic polymers as latex, polyurethane, and polystyrene. Dynabeads® superparamagnetic polystyrene beads are only one example.

The Examiner further notes that Dynabeads® DNA DIRECT is "identified [in the specification] exclusively by its tradename, . . . [which] is inadequate as a written description." In view of this comment, applicants amended the specification to specify that Dynabeads® are superparamagnetic polystyrene beads.

The specification as filed states, at page 23, lines 2-4, that Dynabeads® DNA DIRECT contains beads equivalent to Dynabeads® M-280*, i.e, Dynabeads® that are about 2.8 μM in diameter.

The examiner also alleges that the specification provides enablement only for a DNA purification method using Dynabeads®, and "does not reasonably provide enablement for any other support or even any hydrophobic support" (see the Office Action at page 2, second paragraph). The examiner's rationale is that "detergents typically disrupt hydrophobic interactions upon which, the examiner believes, this method is based." However, as noted in the specification at page 12, lines 25 and 26, nucleic acid binds to the solid support by "hydrogen bonding or ionic or other forces." As quoted above, the specification discloses that "positively charged surfaces, weakly negatively charged neutral surfaces and hydrophobic surfaces . . . have been shown to work well" (emphasis added). Thus, the Examiner's belief is groundless.

The Examiner does not explain why the specification is not enabling for solid supports that are not hydrophobic. The use of Dynabeads® or Dynabeads® DNA DIRECT beads in the working examples does not mean that only these products can be used. On the contrary, these working examples (13 in total) provide ample guidance to a skilled artisan on how to use the other supports disclosed in the specification in achieving nucleic acid isolation.

Dynabeads® and Dynabeads® DNA DIRECT

The Examiner requests information about whether Dynabeads® superparamagnetic polystyrene beads used in the disclosed examples are a product of the prior art. As stated in

the *Declaration of Arne Deggerdal under 37 C.F.R. § 1.131* (submitted herewith), the Dynabeads® product was first offered for sale in the United States by Dynal AS in August 1986. A copy of the manufacturer's instruction provided to U.S. users of this product is attached to the *Declaration* as Exhibit A. Mr. Deggerdal is a co-inventor of the present application, and is employed by Dynal AS, the assignee of the present application.

The Dynabeads® DNA DIRECT kit, which contains Dynabeads® DNA DIRECT superparamagnetic polystyrene beads, is a kit of the invention and is not a product of the prior art. As stated in the enclosed *Declaration*, the kit was first offered on sale in the United States by Dynal AS in June 1995. This date was less than one year prior to the international filing date (December 12, 1995) of this application.

Rejection under 35 U.S.C. § 103(a)

Claims 1-12 and 14-18 are further rejected as allegedly obvious over Woodard et al. (U.S. Patent No. 5,329,000). According to the examiner, Woodard teaches the use of silicon tetrahydrazide to bind and thereby isolate DNA. The examiner also states that, although the reference does not teach the use of detergents, such use is common in cell lysis procedures. Cashion is not relied on but is cited as an example in which nucleic acids are bound to a hydrophobic support.

Applicants traverse this rejection. Claim 1, the only independent claim, is first discussed. The claim, as amended, requires that the solid support contain an organic polymer such

as latex, polyurethane or polystyrene. This requirement is not rendered obvious by Woodard.

Woodard states at column 2, lines 24-28:

> The invention can be used to purify DNA from a variety of sources and from a variety of forms. The process uses the composition of the invention and renders the use of binding buffers, such as chaotropes, optional.

That "composition of the invention" is silicon tetrahydrazide. It is clear that Woodard's method for isolating DNA requires the use of a particular composition. This composition is the core of Woodard's invention. Indeed, Woodard describes in length this composition and the process for making this composition. See, e.g, column 2, line 40, through column 4, line 24, and Example 1. Woodard does not suggest the use of any other materials for binding nucleic acids. By means of this silence and the explicit teaching of using a specific composition, Woodard in fact discourages the use of any other materials for binding nucleic acids without chaotropes.

Further, Woodard's composition for DNA binding is nitrogen- and silicon-based, while the support in the claimed method contains a carbon-based (i.e., organic) polymer. Given Woodard's disclosure, a skilled artisan would not have had a reasonable expectation that a carbon-based polymer can be used to bind nucleic acids in the absence of chaotropes.

Applicants further point out that Cashion, cited but not relied on by the Examiner, teaches away from the invention. In Cashion's method for nucleic acid isolation, the binding of

nucleic acids to the solid support is sensitive to detergents. See column 4, lines 19-21. Thus, according to Cashion, the nucleic acid-containing solution should be essentially free of detergents for the binding to a solid support to occur. In the claimed method, however, binding of nucleic acid to a solid support occurs in the presence of a detergent.

In conclusion, claim 1 is distinguishable over the cited art. For the same reasons, claims 2-12, 14-18, and new claims 19-24 are also distinguishable over the cited art.

Applicants note that claim 13 was not rejected over any prior art.

CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that the claims, as now pending, define subject matter that is both enabled and nonobvious over the prior art. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

A Petition for Extension of Time and a check covering the extension fee and the excess claims fee are enclosed herewith.

Please charge any additional fees, or apply any

credits, in this matter to Deposit Account No. 06-1050, referencing attorney docket no. 08269/003001.

Respectfully submitted,

Reg. No P42,000

Date: 5/19/1998

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